

A Contribution to the Etiology of Neurogenic Extraocular Palsy

Inaugural-Dissertation

zur Erlangung der Doktorwürde
der Medizinischen Fakultät der Universität Basel

vorgelegt von

HARVEY TAUBES

von New York (USA)



19

60

Verlag von S. Karger in Basel

1958

Von der Medizinischen Fakultät genehmigt auf Antrag von
Prof. Dr. med. *F. Rintelen*.

Tag der Promotion: 5. Dezember 1958.



Sonderdruck aus «Confinia Neurologica» Vol. 20, No. 1, 1960

Aus der ophthalmologischen Klinik und Poliklinik der Universität Basel
(Vorsteher: Prof. Dr. med. *Friedrich Rintelen*)

A Contribution to the Etiology of Neurogenic Extraocular Palsy

By Harvey TAUBES

Isolated paralysis of the extrinsic ocular muscles is not an infrequent occurrence in older persons who show evidence of hypertension or generalized arteriosclerosis [1]. The etiology of these palsies is presumed to be hemorrhage or softening in the area of the muscle nuclei or along the intracerebral pathway of the nerve fibers on the basis of corresponding vascular lesions. Often these paralyzes tend to be transitory and at times proceed to complete clinical recovery within a period of weeks to months.

Vascular lesions of the brain stem, however, are usually associated with syndromes corresponding to the area affected, such as oculomotor palsy with contralateral hemiplegia (Weber's syndrome), abducent nerve palsy with paralysis of gaze to the side of the lesion (Foville's syndrome), or abducent and facial nerve palsy with crossed hemiplegia (Millard-Guber's syndrome). The fact that these syndromes are usually absent in the aforementioned isolated palsies indicates that the intracerebral location of the vascular lesion is doubtful.

The object of this study is to show that perhaps many of these isolated paralyzes may be caused by vascular changes in the nutrient arteries supplying the extracerebral nerve fibers of the third, fourth and sixth cranial nerves.

The Blood Supply of the Third, Fourth and Sixth Cranial Nerves

In reviewing the literature one finds that although a substantial number of anatomical papers have been written on the blood supply

of peripheral nerves, little space has been devoted to the cranial nerves.

In 1928, Grigorowsky [2] injected the blood vessels of 10 children and 2 adults who came to autopsy and then dissected the blood supply to the cranial nerves. He showed that the nutrient artery divides into an ascending and descending branch before it enters the epineurium or after it has penetrated the nerve. Then it usually gives off small branches which penetrate the perineurium and which end in a network of arterioles and capillaries that lie between and within the nerve bundles. The number of branches to a nerve and their origins are variable. Usually the cranial nerves are supplied by more than one artery.

He also found that the ophthalmic artery supplies the orbital part of the third, fourth and sixth cranial nerves with nutrient rami, whereas the cavernous sinus portion of these nerves get their nutrient arteries from the internal carotid artery. Before entering the cavernous sinus the abducent and oculomotor nerves get their own nutrient supply from fine branches of the basilar and posterior communicating arteries. No mention was made of the nutrient rami of this portion of the trochlear nerve.

Dreyfus et al. [3] obtained similar results except for the blood supply of the intracavernous part of the oculomotor nerve. They did not find any branches coming from the internal carotid artery at post mortem examination in four cadavers. To help clarify this, they injected Neoprene into the common carotid arteries of rabbits and cats and observed that in these animals this portion to the third cranial nerve is at times supplied by a small branch of the external carotid or the middle meningeal artery and not from the internal carotid artery. This would also confirm the variability of the origins of the nutrient arteries to these cranial nerves.

Methods and Materials

Selection of Material: Unfortunately autopsy material from cases of the corresponding muscle palsies was not available. Therefore, it was decided, that the nerve sections would be taken from the cadavers of 25 older persons who at autopsy showed evidence of hypertensive or arteriosclerotic disease, to see if the nutrient arteries of the oculomotor, abducent or trochlear nerves showed the corresponding vascular lesions, with the feeling that such changes could account for many cases of isolated extraocular ophthalmoplegia previously diagnosed as of "undetermined origin". This group was then divided into four sub-groups according to age. Those in sub-group (a) were 60-65 at the time they came to autopsy, sub-group (b) 66-70, those in subgroup (c) were 71-75, and those in sub-group (d) 76-80.

A control series was made with nerve sections taken from autopsy material of 5 younger individuals ranging in age from 20-35, all of whom showed no evidence of arteriosclerosis or other vascular disease.

Technique: A one centimeter piece of the left and right third, fourth and sixth cranial nerves was removed at that point at which each of these pierces the dura mater to enter the cavernous sinus. The nerves were fixed in formalin and subsequently embedded in paraffin. Serial sections were made and these were stained with hematoxylin and eosin and van Gieson stain.

Results

Of the 25 cases ranging in age from 60–80, 7 revealed histologic evidence of arteriosclerosis of the nutrient arteries of the nerve sections taken. A summary of the results is shown in Table I.

TABLE I

Group	Age	No. of cases	Autopsy evidence of arteriosclerotic disease	Sclerosis of nutrient artery of 3rd, 4th or 6th nerve
I (a)	60–65	5	5	1
(b)	66–70	7	7	3
(c)	71–75	6	6	1
(d)	76–80	7	7	2
	Total	25	25	7
Control II	20–35	5	0	0

The degree of sclerosis of the nutrient rami varied from an increase in adventitial collagen with scattered perivascular lymphocytes, to an eccentric thickening and hyalinization with proliferation of endothelial cells in the intima. In one case the nutrient arteries of all 3 nerves showed these changes. In another case the nutrient rami of the third and sixth nerve showed vessel wall changes. In the other five cases showing sclerosis it was observed in the nutrient vessels of only one of the 3 nerves taken. The nerves themselves were intact with the exception of case 3, in which there was an increase in peri- and epineural connective tissue. In all of these cases, as mentioned previously, there was, however, no clinical evidence of extraocular palsy. Table 2 summarizes the microscopic findings in the cases showing nutrient artery sclerosis. The nutrient vessels in the other 18 cases were physiological.

Clinical Study

A careful review of the case histories of the patients seen in the out-patient division of the Basel University Eye Hospital was made to determine the frequency of acquired paralyses of the extraocular muscles which are innervated by the third, fourth and sixth cranial nerves. During the five year period from 1953 through 1957, 388 cases of extraocular muscle palsy were diagnosed. The number seen each year is presented in Table III.

TABLE II
*Summary of Microscopic Findings in the Cases
 Showing Nutrient Artery Sclerosis*

Case No.	Age	Sex	Nerve involved
1	64	F	3, 4 and 6
2	66	M	3
3	66	F	6
4	70	M	6
5	74	M	6
6	77	M	4
7	79	F	3 and 6

TABLE III
*Cases of Extraocular Palsy at the Basel University Eye Hospital
 Outpatient Clinic from 1953 through 1957*

Year	Total cases	No. of cases of paralysis
1953	11,032	67
1954	11,831	75
1955	13,252	89
1956	13,475	85
1957	13,967	72
Total	63,557	Total 388

The majority of these paralyses were of traumatic etiology, but a significant number each year were of probable "extracerebral vascular origin" as is shown in Table 4.

TABLE IV
Major Etiologies of Paralysis

Etiology	1953	1954	1955	1956	1957
Trauma	26	33	39	26	31
Vascular					
(a) cerebral	11	10	18	9	6
(b) extracerebral	8	4	8	15	4
Inflammatory	6	6	3	3	3
Multiple Sclerosis	3	4	2	5	6
Tumors	4	5	10	5	8
Miscellaneous	5	6	7	20	7
Unknown	4	7	2	2	7
Totals	67	75	89	85	72
Grand total 388					

This diagnosis was made in conjunction with clinical evidence of hypertensive disease, diabetes, or arteriosclerotic disease and after a careful neurological examination was completed at the Neurological out-patient clinic of Basel to rule out cerebral vascular accident. Of the 39 patients in whom this diagnosis was made, all were past 55 years old when first seen for diplopia of sudden onset, except 2, who were 43 and 52 respectively (Table V).

TABLE V

Age at Diagnosis of Extraocular Palsy of Extracerebral Vascular Origin

Age	No. of cases
40-55	2
56-65	10
66-75	23
76-85	4
Total	39

In 16 of the cases follow up examinations to evaluate the rate and degree of recovery of the muscle involved revealed disappearance of the diplopia.

Discussion

The possibility of vascular occlusion of the nutrient arteries as an etiology of paralysis of the third, fourth and sixth cranial nerve has often been disputed. However, the demonstration of vascular disease elsewhere in the body as a cause of nerve degeneration, would favor this view.

Roberts [4] showed, that although the blood supply of nerves is very abundant, obliteration of the nutrient vessels by various methods alters the function and structure of the nerves. It has also been shown that acute ischemia of a peripheral nerve caused marked degeneration of the myelin sheath and the axis cylinder [5]. However, if the vascular insufficiency was chronic, the nerve fibers remained intact, but the epineural connective tissue appeared thickened, infiltrated and edematous [6]. Identical changes were found by *Panzenko* [7], *Barker* [8] and *Priestley* [9]. *Priestley* also observed that the degeneration of the nerve fibers was proportional to the degree of arteriosclerosis. *Woltmann and Wilder* [10] found arteriosclerosis

of the nutrient arteries on histologic examination of the peripheral nerves at autopsy in 6 of 10 diabetics who had neurological signs clinically. One of these also showed marked degeneration of the nerve.

In a case of oculomotor nerve palsy and diabetes, histologic lesions of the nerve parenchyma and interstitial tissue of the retroorbital part of the nerve were found at autopsy. Although serial sections of the nerve failed to demonstrate an occluded vessel, the authors postulated the possibility of occlusion of a nutrient artery outside the nerve [3].

In the present study 7 cases showed arteriosclerosis of the intra- and subepineural vessels histologically, although no clinical evidence of muscle paralysis was present. It is probable that a sufficient blood supply was still carried by these vessels to prevent ischemic degeneration of the nerves.

An analysis of a previous study [11] at the Basel University Eye Hospital on the incidence and etiology of extraocular palsy revealed that the major causes are essentially the same today as they were 20 years ago. Two points of interest were brought out in comparing the two studies. The first was the decrease in the number of cases of unknown etiology. 15 % of the 233 cases in the study by *Kessler* [11] had this diagnosis, whereas only 5 % of the 388 cases in the present study. The second was that the extracerebral vascular etiology was neglected entirely in her study, whereas this diagnosis was made in 10 % of the cases in our study. This can only be explained by the doubt as to the existence of this entity as a cause of extraocular muscle paralysis. This doubt still exists today as can be seen when reviewing pathologic and clinical literature on the etiology of extraocular palsy [12-16]. Although a variety of vascular diseases are always discussed, among them aneurysms of the carotid interna or pressure atrophy of a nerve due to arteriosclerosis of the adjacent vessel [12, 15], there is always the significant omission of paralysis caused by arteriosclerosis of the nutrient arteries of the nerves themselves. Perhaps, with the knowledge that arteriosclerosis of the nutrient arteries does occur and by performing more frequent post mortem microscopic examinations in cases of extraocular muscle paralyzes of unknown origin, more cases of nutrient artery sclerosis will be diagnosed.

The incidence of involvement of each of the three nerves in the present study was approximately the same as that of the earlier study [11], and also that of *Tanobe* [17]. Of the 388 cases the oculo-

motor nerve was involved in $178 = 45.8\%$, the trochlear nerve in $41 = 10.6\%$ and the abducent nerve in $169 = 43.6\%$ of the cases.

Summary and Conclusions

The nutrient vessels of the third, fourth and sixth cranial nerves of 25 cadavers of arteriosclerotic individuals were examined histologically. Arteriosclerosis was present in 7 cases.

The records of 388 patients seen during a five year period at the Basel University Eye Hospital for acquired paralysis of eye muscles were reviewed. 39 cases were of probable extracerebral vascular origin. 37 of these occurred in patient over 55 years old. The diplopia disappeared in 16 of the 39 cases.

It is concluded that arteriosclerosis of the nutrient vessels of the third, fourth and sixth cranial nerves does occur.

The diagnosis of "extrinsic eye muscle paralysis of extracerebral vascular origin" should be suspected in cases of isolated muscle paralysis in older persons with evidence of arteriosclerotic disease.

Zusammenfassung

Es wurden die Vasa nutritia des dritten, vierten und sechsten Gehirnnerven von 25 arteriosklerotischen Patienten histologisch untersucht; bei 7 wurde eine Arteriosklerose gefunden.

Die Krankengeschichten von 388 Patienten mit Augenmuskellähmungen, die während der letzten fünf Jahre in die Universitäts-Augenpoliklinik Basel kamen, wurden durchgesehen. In 39 Fällen war eine extracerebrale vaskuläre Ursache wahrscheinlich; 37 davon betrafen Patienten über 55 Jahre.

Es darf angenommen werden, daß eine Arteriosklerose der Vasa nutritia des dritten, vierten und sechsten Gehirnnerven bei älteren Patienten mit Zeichen allgemeiner Arteriosklerose für isolierte Augenmuskellähmungen ursächlich in Frage kommt. Ihre Prognose scheint relativ gut, insofern als bei 16 von 39 Patienten mit solchen Paresen sich die Lähmung in verhältnismäßig kurzer Zeit zurückbildete.

Résumé

L'auteur a examiné chez 25 malades artériosclérotiques, les vasa nutritia du 3^e, 4^e et 6^e nerf crânien; chez 7 d'entre eux il a trouvé une artériosclérose.

Les observations de 388 malades atteints de paralysie des muscles oculaires, qui avaient été examinés pendant les cinq dernières années à la Policlinique universitaire d'ophtalmologie de Bâle, ont été revues.

Sur les 39 cas, chez lesquels une origine extravasculaire était probable, 37 concernaient des malades âgés de plus de 55 ans.

L'auteur conclut qu'une artériosclérose des vasa nutritia des nerfs crâniens en question, chez des malades atteints d'artériosclérose généralisée, peut provoquer une paralysie isolée des muscles oculaires.

Etant donné que chez 16 des 39 malades, les parésies musculaires ont régressé dans un laps de temps relativement court, le pronostic semble relativement favorable.

Bibliography

1. Rintelen, F.: Personal Communication.
2. Grigorowsky, I. M.: Zur Anatomie der die Kopfnerven ernährenden Arterien. *Z. Anat. EntwGesch.* 87: 728 (1928).
3. Dreyfus, P. M.; Hakim, S. and Adams, R. D.: Diabetic ophthalmoplegia. *Arch. Neurol. Psychiat.*, Chicago 77: 337-349 (1957).
4. Roberts, J. T.: The effect of occlusive arterial diseases of the extremities on the blood supply of nerves. *Amer. Heart J.* 35: 369-392 (1948).
5. Lapinsky, M.: Über Veränderungen der Nerven bei akuter Störung der Blutzufuhr. *Dtsch. Z. Nervenheilk.* 15: 364 (1899).
6. Lapinsky, M.: Zur Frage der Veränderungen in den peripherischen Nerven bei der chronischen Erkrankung der Gefäße der Extremitäten. *Dtsch. Z. Nervenheilk.* 13: 468 (1898).
7. Pancenko, P.: Über den Einfluß der Ischämie auf die peripheren Hirnstämme. *Ann. Anat. path.* 17: 61-69 (1947).
8. Barker, N. W.: Lesions of peripheral nerves in thromboangiitis obliterans. A clinico-pathologic study. *Arch. intern. Med.* 62: 271 (1938).
9. Priestley, J. B.: Histopathologic characteristics of peripheral nerves in amputated extremities of patients with arteriosclerosis. *J. nerv. ment. Dis.* 75: 137 (1932).
10. Woltman, H. W. and Wilder, R. M.: Diabetes mellitus: Pathologic changes of the spinal cord and peripheral nerves. *Arch. intern. Med.* 44: 576 (1929).
11. Kessler, E.: Über Häufigkeit, Ätiologie und Prognose der Augenmuskellähmungen. *Confin. Neurol.* 4: 159-171 (1941).
12. Bielschowsky, A.: Handbuch der ges. Augenheilkunde von Gräfe-Sämisch. Bd. 8, 1. Abt., 433-457 (1939).
13. Bernheimer, S.: Handbuch der ges. Augenheilkunde von Gräfe-Sämisch. Bd. 8, 1. Abt., 1-98 (1939).
14. Walsh, F. B.: Clinical Neuro-ophthalmology. 2nd edition. 1294 pp. (Williams and Wilkins, Baltimore 1957).
15. Cogan, D. G.: Neurology of the ocular muscles. 214 pp. (Charles G. Thomas, Springfield 1948).
16. Rucker, C. W.; Dyer, T. A.; Smith, D. C. and Taub, R. G.: The causes of acquired paralysis of the ocular muscles. *Amer. J. Ophthal.* 41: 950-958 (1956).
17. Tanobe, T.: cit. by Kessler [11].